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Flash Generation of α-(Trifluoromethyl)vinyllithium and an Application to Continuous Flow Three-Component Synthesis of α-Trifluoromethylamides†

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α-(Trifluoromethyl)vinyllithium was generated and used for the reaction with electrophiles at –78 °C in a flow microreactor although the batch reaction should be carried out at ca. –100 °C, and the method was applied to continuous flow three-component synthesis of α-trifluoromethylamides.

Trifluoromethyl-substituted vinylmetals[1] such as α-(trifluoromethyl)vinyllithium serve as powerful building blocks[2] for constructing CF_3-containing molecules.[3] However, because α-(trifluoromethyl)vinyllithium is very unstable,[4] it should be generated and reacted at extremely low temperatures if we use batch macro reactors. In fact, Tarrant[4a] and Ichikawa[2c] reported independently that the generation of α-(trifluoromethyl)-vinyllithium followed by the reaction with an electrophile should be carried out at ca. –100 °C because of rapid elimination of LiF to give 1,1-difluoroallene. Notably, batch reactions are often carried out using an excess amount of α-(trifluoromethyl)-vinyllithium, and the yields are usually reported based on the amounts of electrophiles. Here, we show that flash chemistry[5,6] using flow microreactor systems[7,8,9] enables the generation and reactions of α-(trifluoromethyl)vinyllithium at more easily accessible temperatures to give the desired products in good yields without using an excess amount of the lithium reagent. We also report here that the method enables continuous flow three-component synthesis[10,11,12] of α-trifluoromethylamides,[13] which serve as fascinating motifs in peptidomimetics.

A flow microreactor system consisting of three T-shaped micromixers (**M1**, **M2** and **M3**) and three microtube reactors (**R1**, **R2** and **R3**) shown in Figure 1 was used for Br/Li exchange of 2-bromo-3,3,3-trifluoropropene with *s*-BuLi to generate α-(trifluoromethyl)vinyllithium followed by reactions with electrophiles.

First, we examined the reaction using benzaldehyde as an electrophile, and the desired product was obtained in a good yield (79%) based on 2-bromo-3,3,3-trifluoropropene at –78 °C (Table 1). The reactions with other aldehydes also gave the corresponding products in good yields as shown in Table 1. Thus, the flash method enables efficient generation and use of α-(trifluoromethyl)vinyllithium at easily accessible conditions.

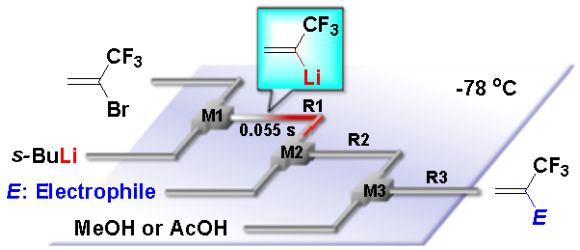
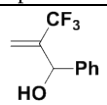
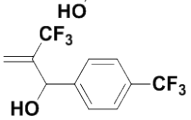
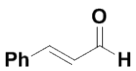
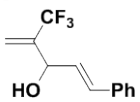
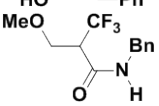
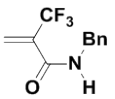
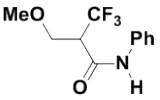
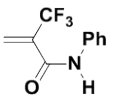
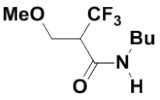
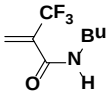


Fig. 1 A flow microreactor system for generation of α-(trifluoromethyl)vinyllithium followed by reactions with electrophiles and the subsequent quenching with methanol or acetic acid. T-shaped micromixers: **M1**, **M2** and **M3**, microtube reactors: **R1**, **R2** and **R3**.

Table 1 Reactions of α-(trifluoromethyl)vinyllithium with various electrophiles.

electrophile	quenching agent	product	yield (%)
PhCHO	MeOH		79
(*p*-CF_3)PhCHO	MeOH		72
	MeOH		90
O=C=N-Bn	MeOH		80
	AcOH		62
O=C=N-Ph	MeOH		65
	AcOH		63
O=C=N-Bu	MeOH		83

AcOH		72

The reactions with isocyanates are interesting. Quenching with methanol gave the compounds having a methoxy group, although the use of acetic acid as a quenching agent gave the desired alkenes having CF_3 and amide groups in good yields (Table 1).

The formation of the compounds having a methoxy group can be explained by deprotonation of methanol by the initially formed lithium amide followed by the addition of the methoxide ion to the carbon-carbon double bond activated by the electron withdrawing CF_3 and amide groups. This explanation leads to the idea of using carbon nucleophiles having an acidic proton instead of methanol (Figure 2). The lithium amide deprotonates a subsequently added carbon nucleophile (Nu-H), and the resulting carbanion ($Nu^- Li^+$) adds to the electron-deficient carbon-carbon double bond. Protonation gives the corresponding three-component coupling products.

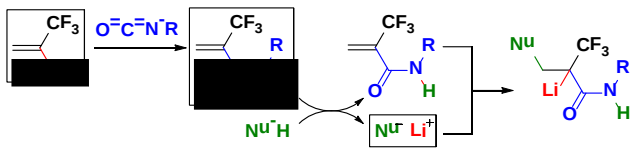


Fig. 2 The reaction of α-(trifluoromethyl)vinyllithium with an isocyanate followed by the reaction with a subsequently added nucleophile.

We chose to use malonate esters as carbon nucleophiles. Thus, the Br/Li exchange of 2-bromo-3,3,3-trifluoropropene, the reaction of the resulting α-(trifluoromethyl)vinyllithium with an isocynate, and the subsequent reaction with a malonate ester were integrated[14] using a flow microreactor system consisting of four T-shaped micromixers (**M1**, **M2**, **M3** and **M4**) and four microtube reactors (**R1**, **R2**, **R3** and **R4**) shown in Figure 3.

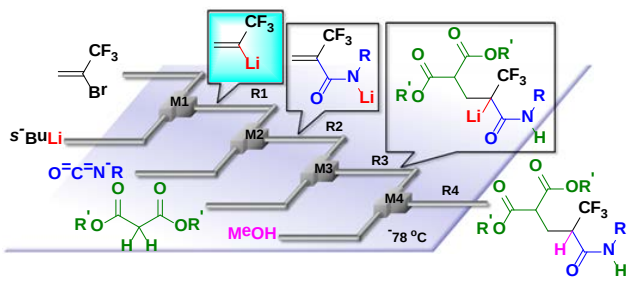
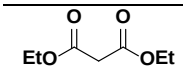
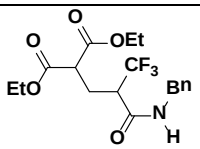
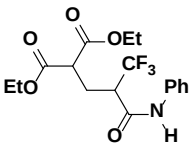
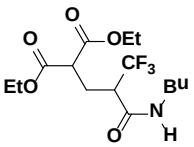
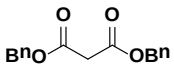
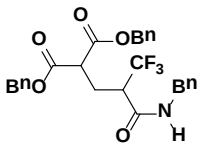
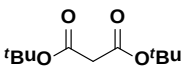
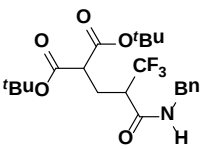


Fig. 3 An integrated flow microreactor system for generation of α-(trifluoromethyl)vinyllithium followed by the reactions with isocyanates and subsequently added malonate esters. T-shaped micromixers: **M1**, **M2**, **M3** and **M4**, microtube reactors: **R1**, **R2**, **R3** and **R4**.

As shown in Table 2, the integration of the reactions was successfully achieved with diethyl malonate, dibenzyl malonate, and di-*tert*-butyl malonate to obtain the corresponding addition products in good yields, although the use of 1,3-diketones such as 2,4-pentanedione did not give the desired products.

Table 2 Three-component coupling of α-(trifluoromethyl)vinyllithium, isocyanate, and malonate esters.

malonate ester	isocyanate	product	yield (%)
	O=C=N-Bn		80
	O=C=N-Ph		65
	O=C=N-Bu		73
	O=C=N-Bn		51
	O=C=N-Bn		66

In conclusion, flash chemistry enables efficient generation of α-(trifluoromethyl)vinyllithium and its reactions with electrophiles at –78 °C. Space integration of reactions enabled three-component synthesis of α-trifluoromethylamides by successive reactions of α-(trifluoromethyl)vinyllithium with isocyanates and malonate esters. The key to the success of the three-component coupling is deprotonation of malonate esters by the lithium amide intermediates followed by the nucleophilic attack of the resulting carbanions on the carbon-carbon double bond activated by the CF_3 and the amide groups. This mode of reaction integration adds a new dimension to continuous flow multicomponent coupling.[15] Further applications of the present method to the continuous-flow synthesis of fluorine-containing organic compounds[16] are currently in progress in our laboratory.

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Notes and references

[1] Reviews on reactions of α-(trifluoromethyl)vinyl compounds: (*a*) K. Uneyama, Organofluorine Chemistry, Blackwell, Oxford, 2006; (*b*) M. Shimizu and T. Hiyama, *Angew. Chem., Int. Ed.*, 2005, **44**, 214; (*c*) J. M. Percy, *Top. Curr. Chem.*, 1997, **193**, 131; (*d*) P. Lin and J. Jiang, *Tetrahedron*, 2000, **56**, 3635; (*e*) H. Ito, *Adv. Polym. Sci.*, 2005, **172**, 37; (*f*) H. Ito, H. D. Truong, M. Okazaki and R. A. DiPietro, *J.*

Photopolym. Sci. Technol., 2003, **16**, 523.

[2] (*a*) K. Iseki, Y. Kuroki, T. Nagai and Y. Kobayashi, *J. Fluorine Chem.*, 1994, **69**, 5; (*b*) Q. Chen and F. L. Qing, *Tetrahedron*, 2007, **63**, 11965; (*c*) R. Nadano, K. Fuchibe, M. Ikeda, H. Takahashi and J. Ichikawa, *Chem. Asian J.*, 2010, **5**, 1875; (*d*) H. Lebel, M. Davi and G. T. Stoklosa, *J. Org. Chem.*, 2008, **73**, 6828; (*e*) V. De Matteis, F. L. van Delft, J. Tiebes and F. P. J. T. Rutjes, *Synlett*, 2008, 351; (*f*) T. Yamazaki and N. Ishikawa, *Chem. Lett.*, 1984, **13**, 521; (*g*) B. Jiang and Y. Xu, *J. Org. Chem.*, 1991, **56**, 7336; (*h*) Y. Xu, F. Jin and W. Huang, *J. Org. Chem.*, 1994, **59**, 2638; (*i*) B. Jiang, Q. Wang, C. Yang and M. Xu, *Tetrahedron Lett.*, 2001, **42**, 4083; (*j*) R. Pan, X. Liu and M. Deng, *J. Fluorine Chem.*, 1999, **95**, 167; (*k*) C. M. Hu, F. Hong and Y. Y. Xu, *J. Fluorine Chem.*, 1993, **64**, 1; (*l*) S. Peng and F. L. Qing, *J. Chem. Soc. Perkin Trans. 1*, 1999, 3345; (*m*) F. Hong, X. Tang and C. Hu, *J. Chem. Soc. Chem. Commun.*, 1994, 289; (*n*) Q. Chen and F. L. Qing, *Tetrahedron*, 2007, **63**, 11965; (*o*) I. Nowak and M. J. Robins, *J. Org. Chem.*, 2007, **72**, 2678; (*p*) T. Konno, J. Chae, T. Tanaka, T. Ishihara and H. Yamanaka, *J. Fluorine Chem.*, 2006, **127**, 36; (*q*) T. Hanamoto, N. Morita and K. Shindo, *Eur. J. Org. Chem.*, 2003, 4279; (*r*) T. Kobayashi, T. Eda, O. Tamura and H. Ishibashi, *J. Org. Chem.*, 2002, **67**, 3156; (*s*) X. Liu, M. Shimizu and T. Hiyama, *Angew. Chem., Int. Ed.*, 2004, **43**, 879; (*t*) T. Yamazaki, T. Kawasaki-Takasuka, A. Furuta and S. Sakamoto, *Tetrahedron*, 2009, **65**, 5945.

[3] (*a*) Modern Fluoroorganic Chemistry: Synthesis Reactivity, Applications (Ed.: P. Kirsch), Wiley-VCH: Weinheim, 2004; (*b*) Fluorine and Health: Molecular Imaging, Biomedical Materials and Pharmaceuticals (Eds.: A. Tressaud and G. Haufe), Elsevier: Amsterdam, 2008.

[4] (*a*) F. G. Drakesmith, O. J. Stewart and P. Tarrant, *J. Org. Chem.*, 1968, **33**, 280; (*b*) W. R. Dolbier, Jr. C. R. Burkholder and C. A. Piedrahita, *J. Fluorine Chem.*, 1982, **20**, 637.

[5] Flash chemistry is defined as a field of chemical synthesis where extremely fast reactions are conducted in a highly controlled manner to produce the desired compounds with high selectivity: (*a*) J. Yoshida, *Flash Chemistry. Fast Organic Synthesis in Microsystems*; Wiley-Blackwell, 2008; (*b*) J. Yoshida, A. Nagaki and T. Yamada, *Chem. Eur. J.*, 2008, **14**, 7450; (*c*) J. Yoshida, *Chem. Rec.*, 2010, **10**, 332; (*d*) J. Yoshida, Y. Takahashi and A. Nagaki, *Chem. Commun.*, 2013, **49**, 9896.

[6] (*a*) H. Usutani, Y. Tomida, A. Nagaki, H. Okamoto, T. Nokami and J. Yoshida, *J. Am. Chem. Soc.*, 2007, **129**, 3046; (*b*) A. Nagaki, H. Kim and J. Yoshida, *Angew. Chem., Int. Ed.*, 2008, **47**, 7833; (*c*) A. Nagaki, H. Kim and J. Yoshida, *Angew. Chem., Int. Ed.*, 2009, **48**, 8063; (*d*) A. Nagaki, E. Takizawa and J. Yoshida, *J. Am. Chem. Soc.*, 2009, **131**, 1654; (*e*) Y. Tomida, A. Nagaki and J. Yoshida, *J. Am. Chem. Soc.*, 2011, **133**, 3744; (*f*) H. Kim, A. Nagaki and J. Yoshida, *Nat. Commun.*, 2011, **2**, 264.

[7] Books on flow microreactor synthesis: (*a*) W. Ehrfeld, V. Hessel and H. Löwe, *Microreactors*; Wiley-VCH: Weinheim, 2000; (*b*) V. Hessel, S. Hardt and H. Löwe, *Chemical Micro Process Engineering*; Wiely-VCH Verlag: Weinheim, 2004; (*c*) V. Hessel, A. Renken, J. C. Schouten and J. Yoshida, *Micro Precess Engineering*; Wiley-Blackwell, 2009.

[8] Reviews on flow microreactor synthesis: (*a*) K. Jähnisch, V. Hessel, H. Löwe and M. Baerns, *Angew. Chem., Int. Ed.*, 2004, **43**, 406; (*b*) G. N. Doku, W. Verboom, D. N. Reinhoudt and A. van den Berg, *Tetrahedron*, 2005, **61**, 2733; (*c*) J. Yoshida, A. Nagaki, T. Iwasaki and S. Suga, *Chem. Eng. Tech.*, 2005, **3**, 259; (*d*) P. Watts and S. J. Haswell, *Chem. Soc. Rev.*, 2005, **34**, 235; (*e*) K. Geyer, J. D. C. Codée and P. H. Seeberger, *Chem. Eur. J.*, 2006, **12**, 8434; (*f*) A. J. deMello, *Nature*, 2006, **442**, 394; (*g*) H. Song, D. L. Chen and R. F. Ismagilov, *Angew. Chem., Int. Ed.*, 2006, **45**, 7336; (*h*) J. Kobayashi, Y. Mori and S. Kobayashi, *Chem. Asian. J.*, 2006, **1**, 22; (*i*) M. Brivio, W. Verboom and D. N. Reinhoudt, *Lab Chip*, 2006, **6**, 329; (*j*) B. P. Mason, K. E. Price, J .L. Steinbacher, A. R. Bogdan and D. T. McQuade, *Chem. Rev.*, 2007, **107**, 2300; (*k*) B. Ahmed-Omer, J. C. Brandt and T. Wirth, *Org. Biomol. Chem.*, 2007, **5**, 733; (*l*) P. Watts and C. Wiles, *Chem. Commun.*, 2007, 443; (*m*) T. Fukuyama, M. T. Rahman, M. Sato and I. Ryu, *Synlett*, 2008, 151; (*n*) R. L. Hartman and K. F. Jensen, *Lab Chip*, 2009, **9**, 2495; (*o*) J. P. McMullen and K. F. Jensen, *Annu. Rev. Anal. Chem.*, 2010, **3**, 19; (*p*) J. Yoshida, H. Kim and A. Nagaki, *ChemSusChem*, 2011, **4**, 331; (*q*) C. Wiles and P. Watts, *Green Chem.*, 2012, **14**, 38; (*r*) A. Kirschining, L. Kupracz and J. Hartwig, *Chem. Lett.*, 2012, **41**, 562; (*s*) D. T. McQuade and P. H. Seeberger, *J. Org. Chem.*, 2013, **78**, 6384; (*t*) K. S. Elvira, X. C. Solvas, R. C. R. Wootton and A. J. deMello, *Nat. Chem.*, 2013, **5**, 905; (*u*) J. C. Pastre, D. L. Browne and S. V. Ley, *Chem. Soc. Rev.*, 2013, **42**, 8849; (*v*) I. R. Baxendale, *J. Chem. Technol. Biotechnol.*, 2013, **88**, 519; (*w*) L. Malet-Sanz and F. Susanne, *J. Med. Chem.*, 2012, **55**, 4062.

[9] Some selected recent examples: (*a*) D. Cantillo, M. Baghbanzadeh and C. O. Kappe, *Angew. Chem., Int. Ed.*, 2012, **51**, 10190; (*b*) W. Shu and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2012, **51**, 5355; (*c*) F. Lévesque and P. H. Seeberger, *Angew. Chem., Int. Ed.*, 2012, **51**, 1706; (*d*) K. C. Basavaraju, S. Sharma, R. A. Maurya and D. P. Kim, *Angew. Chem., Int. Ed.*, 2013, **52**, 6735; (*e*) C. Brancour, T. Fukuyama, Y. Mukai, T. Skrydstrup and I. Ryu, *Org. Lett.*, 2013, **15**, 2794; (*f*) J. D. Nguyen, B. Reiß, C. Dai and C. R. J. Stephenson, *Chem. Commun.*, 2013, **49**, 4352; (*g*) C. Battilocchio, J. M. Hawkins and S. V. Ley, *Org. Lett.*, 2013, **15**, 2278; (*h*) A. S. Kleinke and T. F. Jamison, *Org. Lett.*, 2013, **15**, 710; (*i*) K. Asano, Y. Uesugi and J. Yoshida, *Org. Lett.*, 2013, **15**, 2398; (*j*) A. Nagaki, D. Ichinari and J. Yoshida, *Chem. Commun.*, 2013, **49**, 3242; (*k*) L. Guetzoyan, N. Nikbin, I. R. Baxendale and S. V. Ley, *Chem. Sci.*, 2013, **4**, 764; (*l*) S. Fuse, Y. Mifune and T. Takahashi, *Angew. Chem., Int. Ed.*, 2014, **53**, 851; (*m*) A. Nagaki, Y. Takahashi and J. Yoshida, *Chem. Eur. J.*, 2014, **20**, 7931.

[10] Reviews on domino, tandem and cascade reactions: (*a*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; (*b*) I. Ryu and N. Sonoda, *Chem. Rev.*, 1996, **96**, 177; (*c*) P. J. Parsons, C. S. Penkett and A. J. Shell, *Chem. Rev.*, 1996, **96**, 195.

[11] Reviews on multicomponent coupling reactions: (*a*) A. Dömling and I. Ugi, *Angew. Chem., Int. Ed.*, 2000, **39**, 3168; (*b*) H. Bienaymé, C. Hulme, O. Oddon and P. Schmitt, *Chem. Eur. J.*, 2000, **6**, 3321; (*c*) I. Ugi, *Pure Appl. Chem.*, 2001, **73**, 187; (*d*) B. Ganem, *Acc. Chem. Res.*, 2009, **42**, 463.

[12] Selected examples of one-pot sequential reactions: (*a*) A. Orita, J. Yaruva and J. Otera, *Angew. Chem., Int. Ed.*, 1999, **38**, 2267; (*b*) A. Orita, N. Yoshioka, P. Struwe, A. Braier, A. Beckmann and J. Otera, *Chem. Eur. J.*, 1999, **5**, 1355; (*c*) P. A. Clarke, S. Santos and W. H. C. Martin, *Green Chem.*, 2007, **9**, 438; (*d*) T. Nokami, H. Tsuyama, A. Shibuya, T. Nakatsutsumi and J. Yoshida, *Chem. Lett.*, 2008, **37**, 942; (*e*) Y. Numata, J. Kawashima, T. Hara and Y. Tajima, *Chem. Lett.*, 2008, **37**, 1018; (*f*) K. Yamaguchi, M. Kotani, K. Kamata and N. Mizuno, *Chem. Lett.*, 2008, **37**, 1258.

[13] CF_3-substituted amides: (*a*) K. Uneyama, O. Morimoto and H. Nanbu, *Tetrahedron Lett.*,1989, **30**, 109; (*b*) J. J. Morris, L. R. Hughes, A. T. Glen and P. J. Taylor, *J. Med. Chem.*, 1991, **34**, 447; (*c*) J. Walkowiak, M. Tomas-Szwaczyk, G. Haufe and H. Koroniak, *J. Fluorine Chem.*, 2012, **143**, 189.

[14] Space integration of reactions: (*a*) S. Suga, D. Yamada and J. Yoshida, *Chem. Lett.*, 2010, **39**, 404; (*b*) A. Nagaki, A. Kenmoku, Y. Moriwaki, A. Hayashi and J. Yoshida, *Angew. Chem., Int. Ed.*, 2010, **49**, 7543; (*c*) J. Yoshida, K. Saito, T. Nokami and A. Nagaki, *Synlett*, 2011, **9**, 1189. (*d*) A. Nagaki, C. Matsuo, S. Kim, K. Saito, A. Miyazaki and J. Yoshida, *Angew. Chem., Int. Ed.*, 2012, **51**, 3245; (*e*) A. Nagaki, Y. Moriwaki and J. Yoshida, *Chem. Commun.*, 2012, **48**, 11211.

[15] (*a*) W. Stacy and M. G. Organ, *J. Comb. Chem.*, 2007, **9**, 14; (*b*) P. R. D. Murray, D. L. Browne, J. C. Pastre, C. Butters, D. Guthrie and S. V. Ley. *Org. Process Res. Dev.*, 2013, **17**, 1192; (*c*) D. T. McQuade and P. H. Seeberger, *J. Org. Chem.*, 2013, **78**, 6384; (*d*) K. S. Nalivela, M. Tilley, M. A. McGuire, and M. G. Organ, *Chem. Eur. J.*, 2014, **20**, 6603. (*e*) J. Wu, J. A. Kozak, F. Simeon, T. A. Hatton, and T. F. Jamison, *Chem. Sci.*, 2014, **5**, 1227.

[16] (*a*) H. Amii, A. Nagaki, and J. Yoshida, Beilstein *J. Org. Chem.*, 2013, **9**, 2793. (*b*) C. B. McPake and G. Sandford, *Org. Process. Res. Dev.*, 2012, **16**, 844.